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RADIUM

EDITED BY
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VOL. VII JULY, 1916 No. 4

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THE PHOEBE A. HEARST FOUNDATION
QUEEN'S PARK

A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

RADIUM

A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY, PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES.

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VOL. VII. JULY, 1916 No. 4

UTERINE HAEMORRHAGES: WITH SPECIAL REFERENCE TO ACTINOTHERAPY.*

By Henry Schmitz, A.M., M.D., F.A.C.S., Chicago.

GENERAL CONSIDERATIONS.

There are two kinds of uterine hæmorrhage: the one which is periodical and associated with the menses is termed menorrhagia (monthly bleeding); the other occurring at irregular intervals and independent of the menstrual flow is known as metrorrhagia (uterine bleeding). The two conditions may be easily differentiated or it may not be possible to discriminate one from the other. But this is not of any clinical importance, as the one may be a degree of the other and we may term both "uterine hæmorrhage." Whether the menstrual flow is too profuse, lasts too long, or is too frequent should be determined by a careful interrogation of the patient, taking into consideration the number of napkins used, the character of the blood (whether arterial or coagulated), the duration of the flow, and finally the determination of the onset of each hæmorrhage.

ETIOLOGY.

The causes of uterine hæmorrhage are (1) accidents of pregnancy, labor, and puerperium; (2) functional derangements of the genital organs without any demonstrable pathology; (3) diseases of the generative organs with a demonstrable pathology; (4) general constitutional or systemic diseases; and (5) vascular disturbances.

The accidents of pregnancy, labor, and puerperium belong to the domain of obstetrics and will not be considered in this paper. Such

*Surgery, Gynecology and Obstetrics, XXII, 719-722, 1916.

disturbances are abortions, either threatened or incomplete, extra-uterine pregnancy, placenta prævia, premature detachment of the placenta, atony of the uterus during or following the placental stage of labor, injuries of the uterus, retained oval membranes, subinvolution, etc. If a uterine hæmorrhage unexpectedly occurs in a married woman, the possibility of an abortion or extra-uterine gestation should always be considered.

The *functional disturbances* of the genital organs depend in all probability on a dysfunction of the internal secretion of the ovaries and other ductless glands. We know from animal experimentation and clinical observation that hormones of certain ductless glands either inhibit or stimulate ovarian internal secretion; for instance hyperpituitarism causes amenorrhœa, and finally sterility and atrophy of the genital organs. Hyperthyroidism is usually accompanied by amenorrhœa, while hypothyroidism is often associated with uterine hæmorrhages. In other words, increased activity of the thyroid gland leads to a decreased activity of the internal secretion of the ovary, and decreased thyroid gland activity results in an hyperfunction of the ovary.

The *diseases of the uterus and adnexa* accompanied by uterine hæmorrhages are: (1) *Circulatory disturbances* resulting in a hyperplasia of the genital organs. They are brought about by (a) trauma and subsequent scar formation, as lacerations of the cervix, inflammatory cicatrices from necrosis and gangrene, hæmatorma, and hæmatocele; (b) displacements and deformities, as flexions, versions, rotations, torsions, inversion, prolapse, and hernia formation; (c) tumors, leading to an obstruction of the blood and lymph virculation; (d) obstinate and habitual constipation; and (e) active hyperæmia from perversions of sexual and marital life. (2) *Inflammations* of the pelvic organs as gonorrhœal, septic, and tuberculous infection. (3) *New-growths* of the uterus as carcinoma, sarcoma, chorio-epithelioma, myoma and adenomyoma.

General constitutional or systemic diseases are the anæmias (while chlorosis causes oligomenorrhœa or amenorrhœa); chronic poisoning; acute infectious diseases, as cholera, smallpox, malaria, typhoid, and scarlet fever, also scurvy, rheumatoid diathesis and hæmophilia.

Vascular disturbances are the result of chronic cardiac, hepatic, and nephritic disease.

Out of 643 consecutive gynecological cases that came under my observation at the St. Mary's (199) and Willard (444) hospitals, 135 or 21 per cent were accompanied by uterine hæmorrhage due to an underlying genital disease. The diseases associated with uterine hæmorrhage are:

Carcinoma uteri	19 cases	or 14.1	per cent
Chronic adnexitis	16 cases	or 11.8	per cent
Hyperplasia of the endometrium	13 cases	or 9.7	per cent
Myomata uteri	11 cases	or 8.1	per cent
Hyperplasia of myometrium	11 cases	or 8.1	per cent
Retroflexio uteri	11 cases	or 8.1	per cent
Abortion	10 cases	or 7.4	per cent
Descensus uteri	9 cases	or 6.7	per cent
Oophoritis and ovarian tumors	8 cases	or 5.9	per cent
Chronic cervicitis with lacerations	6 cases	or 4.4	per cent

Hæmorrhagic metropathy	6 cases or	4.4 per cent
Extra-uterine pregnancy	5 cases or	3.7 per cent
Endometritis post-abortum	4 cases or	3.0 per cent
Subinvolution of uterus	4 cases or	3.0 per cent
Sarcoma uteri	2 cases or	1.5 per cent

Fifty-six out of these 135 cases are characterized by a proliferation of uterine tissue. Thirty-two or more than one-half of the 56 are caused by new-growths and of these 19 are the result of carcinomatous formations. If we add to these 56 cases the 6 cases of hæmorrhagic metropathy or essential hæmorrhages, we obtain a total of 62 cases which formerly indicated repeated curettages and finally hysterectomies to relieve the patient. The cancers and myomata, of course, were always extirpated if operable.

DIAGNOSIS.

A correct diagnosis of the underlying disease in uterine hæmorrhages is of the utmost importance. It can only be rendered by a microscopic examination of the endometrium or excised pieces of uterine tissue. A careful general and special pelvic examination will be a valuable adjunct. Carelessness in diagnosis leads to procrastination which has often changed a favorable into a hopeless prognosis. Incipient malignancy can only be recognized in this manner. At this stage the malignancy is localized and can be easily and completely eradicated, and an anatomical cure is thus assured.

TREATMENT.

It is not my object to discuss the treatment of the immediate arrest of uterine hæmorrhages at the time of their occurrence or describe the technique of a curettage or of a hysterectomy. The purpose of this study is to call your attention to the curative action of actinotherapy or radiotherapy in treating uterine hæmorrhage. If we subtract from the 62 cases mentioned above the 21 cases of malignancy, we have left 41 cases of uterine hæmorrhage which had existed for a long period of time and resisted all usual treatment. Formerly the majority of these women had to be hysterectomized to bring about a cessation of the hæmorrhage. Six patients were treated with the massive roentgen rays and 12 with radium. The accompanying table gives all the data necessary.

Technique. A course of X-ray treatment consists of 6 seances each of about one hour's duration, given on six succeeding days. Water-cooled tubes of a diameter of 7 inches and a hardness of 7 to 9 Heinz Bauer are charged with a current of 2 to 3 milliamperes. The focal distance of the tube from the patient is 21 cm. The rays are filtered through an aluminum plate of 3 mm. thickness. Six different fields, each 5 cm. square, are drawn upon the suprapubic regions. Thirty to forty X are applied to each field. The amount of X used is determined by a Holzknecht radiometer. The applications are preferably made during the week following the cessation of menstruation. Usually one such course of treatment suffices to produce amenorrhœa. If this should not occur, a second course is given after three weeks, which invariably brings about the desired result. Concomitant symptoms are mild. They usually consist of nausea or diarrhœa, but are of a transient nature.

Only the gamma rays of radium are employed in the treatment of uterine hæmorrhages. The alpha and beta rays are arrested by a lead

Case No.	Name	Age	Civil State	Para	Duration of Hemorrhage	Diagnosis	Date of Treatment
1a	Mrs. G.	56	M.	V	Ten years	Myomata uteri	June 15, 1913
2a	Mrs. S.	47	M.	O	Four years	Myomata uteri	Jan. 20, 1914
3a	Mrs. T.	46	M.	I	Six years	Hyperplasia uteri	Dec., 1913
4a	Mrs. G.	40	M.	V	Three years	Myomata uteri	April 13, 1914
5a	Miss M.	38	S.	O	Several years	Hyperplasia uteri	June 30, 1915
6a	Mrs. K.	48	M.	IV	Eight years	Hyperplasia uteri	May 28, 1914
2	Mrs. N.	45	M.	III	Four months	Myomata uteri	Sept. 21, 1914
42	Mrs. P.	38	M.	O	Six months	Metropathia hemor-	Oct. 28, 1914
44	Mrs. E.	38	M.	IX	One year	rhagica	Nov. 4, 1914
53	Mrs. B.	50	M.	VI	Six years	Myomata uteri	Dec. 7, 1914
72	Mrs. M. E. C.	50	M.	I	Three months	Myomata uteri	Feb. 19, 1915
92	Miss E.	45	S.	O	Three months	Hyperplasia uteri	Mar. 3, 1915
93	Miss C.	39	S.	O	Several years	Metropathia hemor- rhagica	April 6, 1915
95	Mrs. F.	38	M.	III	Two years	Myomata uteri	Feb. 19, 1915
97	Mrs. B.	65	M.	V	Ten years	Myomata uteri Cysto- ma ovarii	May 4, 1915
102	Mrs. P.	32	M.	O	One year	Myomata uteri	May 21, 1915
137	Mrs. D.	45	M.	XII	Three years	Myomata uteri	Sept. 29, 1915
142	Mrs. S.	50	M.	IV	Eighteen days	Hyperplasia uteri	Oct. 8, 1915

filter of the thickness of 2 mm.; the secondary or Sagnac rays, forming in the heavy metal filter, which resemble the soft beta rays of radium, are absorbed by a pure para rubber filter of 1 mm. thickness. The average amount of milligram hours of radium element necessary to cause amenorrhœa is 1,000. If 50 milligrams of radium element are employed, it will take twenty hours to obtain this milligramage. The patient is prepared as for any operation: one-quarter of a grain of morphine is given hyperdermically about one-half hour prior to the time the application is to be made. The field around the vagina is rendered sterile, the cervical canal dilated, the endometrium is curetted for diagnostic purposes, and the radium capsule is then placed in the uterine cavity. A small chain or silk thread is left attached to the capsule to facilitate its removal. On an average 1,000 milligram hours suffice to bring about amenorrhœa. If the patient should still flow at a subsequent period, the application may be repeated after four to six weeks.

I repeat the necessity of a diagnostic curettage to exclude malignancy before the treatment with the roentgen or radium rays is begun.

The *indications* for this treatment followed by me are as follows: Essential uterine hæmorrhages and hyperplasia of endometrium and myometrium. In a patient of 35 years or older, failure of medicinal

Case No.	Kind of Treatment	Immediate Result	Remote Result
1a	X-ray 200-X	Amenorrhoea	Nov. 30, 1915. Well. Mild change of life.
2a	X-ray 300-X	Amenorrhoea	Dec. 4, 1915. Well. Stormy climax.
3a	X-ray 260-X	Amenorrhoea	Nov. 2, 1915. Well. Mild climax. Uterus atrophic.
4a	X-ray 200-X	Amenorrhoea	Mild climax.
5a	X-ray 240-X	Amenorrhoea	Nov. 23, 1915. Well. Mild climax.
6a	X-ray 300-X	Amenorrhoea	Nov., 1915. Well. Severe climax.
2	Radium 1000 mgh.	Amenorrhoea	Well. Mild climax.
42	Radium 1200 mgh.	Amenorrhoea	Nov., 1915. Well. Tumor reduced from child's head to lemon.
44	Radium 1050 mgh.	Amenorrhoea	Nov., 1915, delivered of normal child at full term.
53	Radium 2000 mgh.	Amenorrhoea	Well. Very mild climax.
72	Radium 1150 mgh.	Hemorrhages reappeared	Mar. 8. Hysterectomy. Red degenenration.
92	Radium 2050 mgh.	Amenorrhoea	Nov. 15, 1915, complete Amenorrhoea. Uterus normal.
93	Radium 1800 mgh.	Amenorrhoea	Dec. 2, 1915. Well. Very mild climax.
95	Radium 1250 mgh.	Amenorrhoea	Well. Average climax.
97	Radium 1500 mgh.	Amenorrhoea	Died Nov. 22, 1915, after ovariectomy, but had complete amenorrhoea. Uterus but slightly enlarged. Tumor almost gone.
102	Radium 1200 mgh.	Profuse menses	Tumors are growing. Ought again to be treated.
137	Radium 1600 mgh.	Amenorrhoea	One pedunculated tumor removed. Dec. 1, well.
142	Radium 600 mgh.	Amenorrhoea	Dec. 6, 1915. Amenorrhoea.

and local mechanical treatment to bring about cessation of the hæmorrhages. If repeated curettages in women below 35 years of age do not result in a cure, then actinotherapy is also indicated.

Myomata uteri. Myomata of the cervical submucous or pedunculated varieties and myomata undergoing degenerations must be treated surgically. Women below 35 years of age desiring off-spring are myomectomized. All other myomata are subjected to actinotherapy, which invariably causes amenorrhœa. The tumor decreases in size and often disappears entirely.

Radium is preferable to the X-ray. Radium destroys the endometrium; the roentgen ray causes a cessation of ovarian activity. The symptoms of change of life are, therefore, mild after the former treatment, while they are very pronounced after the roentgen treatment. The latter requires much more time for its application and is more expensive than the use of radium which necessitates an interruption of the daily routine of the patient for only twenty-four hours. Both methods, when property used, are devoid of danger. Should contraindications to surgical measures exist, as heart disease, general constitutional disease, etc., actinotherapy can still be safely and successfully employed.

CONCLUSIONS CONCERNING THE VALUE OF RADIUM-THERAPY IN PERNICIOUS ANAEMIA.

By Frederick Proescher, M.D.

For the critical discussion of the value of radium in pernicious anaemia, a brief recapitulation of the present status of the pathogenesis, diagnosis and therapy of this disease will be given.

The opinion as to the clinical classification of essential pernicious anaemia and its differentiation from other severe anaemias having a pernicious anaemic blood picture, has changed considerably during the last decade.

According to our present knowledge, the essential pernicious anaemia (Addison-Biermer) is a clinical entity characterized by its progressive, sometimes remittent but fatal course of unknown etiology. The former opinion of Ehrlich and Lazarus that the megaloblastic hyperchromatic blood picture (Ehrlich's embryonic blood picture type) caused by a primary disease of the haemopoetic system which is frequently found in this disease and in the most pronounced form, and which should be characteristic of the pernicious anaemia only, is abandoned today. Numerous observations have shown that the blood changes regarded as specific may be temporarily or entirely absent during the entire course of this disease. On the other hand a pernicious anaemic blood picture may be observed undoubtedly in curable and incurable diseases of known etiology as ankylostomasiasis, botricephalus-infection, carcinoma, syphilis, malaria, etc. All pernicious anaemias, including the anaemia which accompanies the morbus Biermer, are all secondarily symptomatic, not primarily essential. Primary essential anaemias do not exist. The anaemia in Biermer's disease, clinically an entity, is the most pronounced symptom and is only secondarily symptomatic. Moreover, all pernicious anaemias are not primary bone marrow diseases or primary myeloid anaemias. The apparently primary bone marrow anaemias (myelo-anaemias) are caused by a metaplasia of the bone marrow and are, therefore, secondary or primary haemolytic or haemotoxic anaemias, like the secondary anaemias. This theory supported by the fact that all banal secondary anaemias may change into a pernicious form proves the latter also to be of secondary nature.

With Pappenheim, I distinctly separate the clinical pernicious anaemia, morbus Biermer, from the pernicious anaemic blood picture. The first is an etiological unknown (kryptogenetic) group of diseases, with a specific clinical course. The latter is a very ominous symptom of different severe toxic anaemias which accidentally received its name from anaemia perniciosa. The pernicious anaemic blood picture is a final and severe symptom of a toxic anaemic regeneration without specific cause, (Schilling-Torgau). The severity of the anaemia depends on the individual resistence to the intoxication (hemotoxin) in which resorption and a partially acquired immunity play an important role. The primary hemotoxin may either be of a serogen or histogen nature (increased local destruction in spleen).

Biermer anaemia, a specific form of the pernicious anaemia, is of unknown origin, probably autotoxic while the botriocephalus anaemia, and carcinoma anaemia if they show the pernicious anaemic blood picture,

are of known etiology. In the case of leukanaemia we do not have a combination of Biermer's disease with leukaemia, but a pernicious anaemia caused by a hyperplasia of the myeloid component of the bone marrow (myeloid anaemia.)

For the diagnosis of pernicious anaemia a careful clinical observation together with repeated blood examinations is necessary to establish the diagnosis of pernicious anaemia during life, but the diagnosis can be made with certainty only post-mortem. The following points are essential for the diagnosis: Characteristic progressive remittent clinical course; exclusion of syphilis, carcinoma, malaria, helminthiasis by specific therapy; presence of a megaloblastic hyperchromatic or hypochromatic blood picture with leukopenia, lymphocytosis and decrease in blood platelets, if only of temporary duration. The difficulty in establishing the diagnosis of essential pernicious anaemia is obvious, and it is, therefore, not surprising to find in the literature a great number of so-called cures of pernicious anaemia, which are in reality nothing else than temporary remissions, but no permanent cures. On the other hand, there are cases recorded where in a curable disease a pernicious anaemic blood picture was found, but a morbus Biermer was diagnosed, which disappeared either spontaneously or under the usual treatment.

All experienced clinicians are convinced that the essential pernicious anaemia is incurable and as long as we are in the dark as to its etiology, the treatment is merely symptomatic. The main therapeutical effort is to increase the red cells or in other words, to stimulate the erythroplastic component of the bone marrow in order to overcome the pathologic destruction of the red cells. As stated above, the essential pernicious anaemia is secondarily haemotoxic, the destruction of the red cells going on extramedullary. The bone marrow, or more exactly, the erythrogenesis is not directly affected. As long as the bone marrow is not exhausted, we may overcome or balance the abnormal destruction by an increased output of red cells.

Of the various therapeutic agents, which stimulate the erythropoesis, iron and arsenic in its various inorganic and organic compounds, are the most valuable. Until the haemostimulating properties of the radioactive substances were discovered, arsenic played the main role in stimulating the red cell formation. Iron as well as arsenic has a direct stimulating effect upon the bone marrow. After the administration of iron Fr. Muller found in animals artificially rendered anaemic an increase in nucleated red cells in the bone marrow. Bettmann and Stockmann found the same for arsenic. Bettmann's careful investigations have shown that arsenic in toxic doses displays two different actions. First: The resistence of the circulating red cells is lowered and the cells therefore, are more rapidly destroyed. Second: The bone marrow shows an over production of premature red cells of increased resistence and the absolute amount of the circulating red cells is considerably increased. In large doses the destructive effect upon the red cells surpasses the stimulating effect and a marked anaemia is the consequence. In conclusion we can say that in minimum and slowly increasing doses the destructive effect upon the circulating red cells is not only completely compensated but surpassed by the production and increased output of newly formed red cells brought into the circulation.

Since Bramwell in 1877 advocated arsenic for the treatment of the progressive anaemia, this drug is used more than any other agent

and as in many cases it has been the sole therapeutic agent, it has gained prestige as a specific. With a few exceptions most authors are inclined to believe that arsenic has a startling beneficial effect as the beginning of recovery corresponds with the administration of this drug. The statistics published by Padley and Fuerbringer seem to speak in favor of the arsenic treatment. Twenty-two cases treated by Padley showed 16 recoveries (?) two improvements and four deaths. Fuerbringer treated fifty-seven cases with the following results. Four relatively recovered, 16 improved, 10 unimproved, and 27 died. The great contrast in both statistics is evident and arouses skepticism that the 16 cases reported recovered were not essential pernicious anaemias. Fuerbringer's statistics show no recovery and speaks merely for a symptomatic but not for a specific influence of arsenic.

A disease with such a variable course, where spontaneous remissions from the most alarming symptoms to an apparent recovery may be observed, lead the inexperienced observer to the most optimistic view as to the therapeutic value of any symptomatic treatment, but in spite of the still doubtful influence of the arsenic upon the course of the pernicious anaemia, we cannot entirely dispute its favorable influence in some cases. It is not my intention to discuss the various arsenic compounds used in the treatment of this disease. I prefer of all arsenic preparations the arsacetin for subcutaneous and intravenous injection, as well as per os. The arsacetin is of all arsenic compounds the most tolerated and I have used it entirely in the last five years without any untoward results such as we experience by the use of inorganic arsenic preparations, and the cacodylates. The solutions can be repeatedly sterilized without deterioration. The methods of preparation and the dosage were described under case No. 1. (This Journal, June, 1916, p. 71).

The increased haemoglobin content of the erythrocytes as well as the great amount of iron stored in the organs, especially in the liver, shows that there is no lack of iron and makes an iron medication unnecessary. The iron therapy is absolutely without any effect in pernicious anaemia.

The treatment of pernicious anaemia with radioactive substances, especially with thorium-X, is of recent date (Plesch, Bickel, Gudzent Klemperer and H. Hirschfeld). Plesch was the first who apparently successfully treated a case of pernicious anaemia with thorium-X. The erythrocytes in this case were only 340,000. After the first intravenous injection of 20,000 mache units, which Plesch designated as "Reizdosis," the red cells increased twenty-four hours later to 1,200,000, on the second day to 1,300,000. On the fifth day the patient again received 20,000 mache units. The blood count on the thirteenth day showed 2,300,000 and on the twenty-third day 3,000,000 red cells. During the treatment the pathological forms of the red cells disappeared and a normal red cell picture was restored. Bickel reported a case of pernicious anaemia in which he obtained a most remarkable result by treatment with thorium-X drinking water, after arsenic treatment had been unsuccessful. The case showed 960,000 red cells, 50% hemoglobin, and 3,800 leucocytes. The patient received 5,000 mache units daily in form of thorium-X drinking water in three portions after each meal for four weeks. Five weeks later a remarkable improvement was noted. The red cells had increased to 6,000,000, the hemoglobin to 90%, and the leucocytes to 8,000.

Hirschfeld and Klemperer (1) treated five cases of pernicious anaemia with intravenous injection of thorium-X and noticed a temporary improvement only in one case. The other cases did not respond to the treatment at all.

In the following tables the five cases of Hirschfeld and Klemperer are given: (Amounts of Thorium-X injected intravenously are expressed in terms of radium bromide).

CASE No. 1.

Date 1912	*Amounts of Thorium-X injected intravenously.*	*Hemoglobin %*	*R. Cells.*	*W. Cells.*
June 13		60	2,700,000	5,800
June 18			2,800,00	4,000
June 19	0.05 mg. Radium bromide equals 40,000 M.U.			
June 22	0.04 mg. Radium bromide equals 40,000 M.U.			
July 4	0.03 mg. Radium bromide equals 30,000 M.U.			
July 12		65	4,100,00	
July 17	0.05 mg. Radium bromide equals 50,000 M.U.			
July 19			4,400,000	

CASE No. 2.

June 3		25	1,300,00	7,400
June 7	20,000 M.U.			
June 8		23	900,000	
June 12			550,000	

CASE No. 3.

April 4		25	1,200,000	
May 2			1,850,000	
May 21	Thorium-X-Injection 0.02 mg. Radium bromide equals 20,000 M.U.			
May 24		35	1,730,000	
May 28		45	1,440,000	
June 1	0.02 mg. Radium bromide equals 20,000 M.U.			
June 2			1,620,000	
June 11		30	1,740,000	
June 19	0.02 mg. Radium bromide equals 20,000 M.U.		1,620,000	
June 15	0.02 mg. Radium bromide equals 20,000 M.U.			
June 24		30	1,020,000	
July 12			950,000	
July 17	0.05 mg. Radium bromide equals 50,000 M.U.			
July 18			1,350,000	

(1) Der jetzige Stand der Thorium-X Therapie mit eigenen Beobachtungen bei Leukamie and Anaemia. G. Klemperer und Hirschfeld. Die Therapie der Gegenwart, 1912.

		Case No. 4.		
May 21		40	1,660,000	
June 19		25	780,000	4,000
June 22	0.02 mg. Radium bromide equals 20,000 M.U.			
June 26		20	428,000	3,000
July 3	0.04 mg. Radium bromide equals 40,000 M.U.			
July 7			470,000	4,300
		Case No. 5.		
June 24		25	1,000,000	4,000
June 28	0.03 mg. Radium bromide equals 30,000 M. U.	20	1,050,000	3,000
July 3	0.12 mg. Radium bromide equals 120,000 M. U.			
July 9		20	800,000	4,880

At the time of the publication of the above table Klemperer and Hirschfeld stated that out of a total of seven cases treated, three were successful and four unsuccessful.

Since the publication of Klemperer and Hirschfeld a number of other authors have reported their results with thorium-X in pernicious anaemia. Most of these case reports confirm to a greater or less degree the observation of these authors. I wish to refer only to the work of Arneth (2) which is by far the most thorough, since a complete analysis of the blood picture was made, especially the leucocyte changes, based on his well known method. The analysis of the blood picture of a pernicious anaemia case twice treated with arsenic, the first treatment responding, while the second failed, and finally given a series of injections with thorium-X is shown in the following table: (Next page).

After the injection of 350,000 mache units of thorium-X the red cells increased over 3,000,000, the hemoglobin to 70%, but both were later somewhat lowered. The leucocytes following the first injection were increased from 1,000 to 2,000 and after three weeks they reached their normal number, 5000 to 6000.

Under the influence of thorium-X the leucocytes were increased from 500 to 600%. At the same time the leucocyte picture was restored to normal. Relatively the lymphocytes decreased from 40% to 19% and the neutrophile leucocytes increased from 53% to 70% The eosinophiles which were abnormally high were slightly decreased and the mononuclear and transitial forms which were entirely absent reappeared.

Arneth concludes that thorium-X influences the blood picture only in a quantitative way. It decreases and increases their production, but in proper dosages does not effect either the white or red cells directly. Thorium-X in pernicious anaemia is a leucocytacticum of a special kind. The normal leucocyte picture is restored by a general movement of the nuclear picture towards the right.

According to the opinion of Klemperer and Hirschfeld, thorium-X has no advantage over the arsenic treatment, as the latter will bring on a remission in about the same percentage of cases as thorium-X. On the other hand they believe that thorium-X will be of value in some

(2) Thorium-X bei pernicioser Anaemie Arneth. Berliner klinische Wochenschrift, 1914, No. 4, p. 153.

Date.	Thorium-X Doramad.	Time A.M.	Erythrocytes.	Hemoglobin per cent.	Leucocytes.
16.6	35	9:45	1,904,000	42	1,000
17.6	..	11:00	1,760,000	47	1,000
19.6	30	11:00	1,428,000	53	2,000
21.6	..	10:15	1,844,000	55	1,400
23.6	35	11:00	1,896,000	57	2,600
25.6	..	11:45	2,224,000	56	3,500
26.6	30				
28.6	..	10:30	2,304,000	62	3,000
30.6	35	11:00	2,424,000	58	
30.6	..	5:45 P.M.	2,176,000	59	
4.7		11:20	2,384,000	57	4,000
8.7		11:30	2,536,000	62	5,200
12.7	35	11:30	2,336,000	65	5,400
16.7		11:00	2,408,000	66	6,700
23.7	30	11:00	2,472,000	68	6,200
28.7		10:45	2,424,000	70	
2.8	30	1:00 P.M.	2,360,000	64	
9.8	30	12:00	2,504,000	70	
14.8	30	1:00 P.M.	2,952,000	70	4,400
20.8	30	11:30	3,064,000	70	4,200
26.8	30	11:00	2,016,000	66	4,100
5.9		11:30	2,400,000	62	6,400
12.9		10:30	2,624,000	62	8,200
19.9		11:00	2,336,000	62	5,800

DIFFERENTIAL COUNT.

Date.	Absolute Leukocyte Count.	Neutrophiles.	Eosinophiles.	Basophiles.	Lymphocites.	Large Mononuclear Cells.	Transital.
16.6	1,000	58	3		38		1
28.6	3,000	48	5	2	45		
16.7	6,700	77	2	0.25	19	0.5	0.75
2.8		63	2	1	34		
26.8	4,100	75	1.6		23		0.4
19.9	5,800	69	0.9	0.3	29	0.3	0.3

BLOOD PICTURE OF RED CELLS.

16.6. Three normoblasts (polychromatic) per 300 leucocytes; in each of three to four fields, one polychromatic erythrocyte, few basophilic erythrocytes (orthochromatic); slight poikilo—and anisocytosis, many microcytes, few megalocytes.

28.6. Slight anisocytosis and a few poikilocytes, no nucleated red cells.

16.7. Very slight anisocytosis and a few poikilocytes.

2.8. Poikilocytosis and anisocytosis in a very slight degree, few megalocytes.

26.8. Anisocytosis almost disappeared; a mere trace of poikilocytosis.

19.9. A mere trace of anisocytosis, normal erythrocytes, very few megalocytes still present.

cases in which arsenic is without influence. They advise treating pernicious anaemia first with arsenic in the form of sodium arsenate or arsacetin. If no effect is noted they advocate the use of tartarus stibiatus (1 to 5 mgm. daily). If both drugs are without effect they advise the use of thorium-X as the ultimum refugium (20 to 40,000 mache units daily). As to the specificity of the thorium-X in pernicious anaemia they express no opinion.

Arneth believes that thorium-X possesses to a certain degree the quality of a specificum for pernicious anaemia, as it temporarily restores the blood picture to normal. Whether or not pernicious anaemia can be definitely cured with thorium-X has as yet not been proven.

At present it is impossible to come to a definite opinion as to the real therapeutic value of the thorium-X treatment in pernicious anaemia. In the majority of the cases a complete analysis of the blood picture with the exception of the case of Arneth was not undertaken and furthermore the observation time in all the cases was too short to reach any definite conclusion as to the advantage over the arsenic treatment and the specific influence of the thorium-X in pernicious anaemia.

If we compare the action of radium with thorium-X in the treatment of pernicious anaemia we notice that both have the same qualitative action, but quantitatively the radium seems far superior to thorium-X. A study of the tabulated cases of Klemperer and Hirschfeld as well as the case of Arneth and both our cases, demonstrates that a single dose of radium produces either the same or a more pronounced effect upon the blood picture than several injections of thorium-X. The leucocyte picture is influenced in the same way as with thorium-X. The slow decay of the radium exerts a more prolonged and on the other hand a more mild action upon the erythrocytes than the rapid decay of thorium-X. According to the investigation of Seil, Viol and Gordon, on the elimination of radium in human beings, from 55 to 65% of the radium intravenously injected remains in the body for four or five days following the injection. The daily rate of elimination of the injected radium 10 days later, is less than 1%. About 35 to 45% of the radium is fixed in the body, mainly in the long bones in form of an insoluble salt giving for a long period a low but fairly constant concentration of radium emanation. The following table demonstrates the distribution of radium salt 108 days after the intravenous injection of one milligram of soluble radium salt intravenously in an inoperable case of carcinoma uteri.

No.	*Part.*	*Wet Weight.*	*Dry Weight.*	*Radium in Sample.*	*Radium Per Gram Dry Weight.*
1.	Heart tissue ..	11.7 gm.	2.26 gm.	.000118 micrograms	0.00005
2.	Aorta tissue abdominal ...	13.4 "	2.79 "	.00219 "	0.00080
3.	Bone marrow (sternum) ..	20.5 "	7.01 "	.04414 "	0.00630
4.	Liver.	11.9 "	2.48 "	.01530 "	0.00610
5.	Suprarenal capsule.	5.3 "	0.91 "	.000118 "	0.00013
6.	Carcinomatous tissue mass of the parametrium	12.4 "	2.17 "	.000275 "	0.00012

7.	Para thyroid gland	0.12	"	0.035	"	Trace?	"	.....
8.	Bone marrow lumbar region	9.18	"	3.73	"	**.01780**	"	**0.00480**
9.	Intestines.	17.7	"	5.10	"	.000700	"	0.00014
10.	Thyroid gland..	13.3	"	2.74	"	.000700	"	0.00026
11.	Kidney.	15.0	"	3.41	"	.000090	"	0.00003
12.	Stomach.	15.5	"	3.30	"	Trace?		.....
13.	Lung.	4.77	"	0.82	"	.00163	"	0.00200
14.	Pancreas.	7.12	"	1.38	"	.00059	"	0.00043
15.	Spleen.	11.83	"	2.90	"	.00196	"	0.00067
16.	Retroperitoneal gland.	26.6	"	11.80	"	.00141	"	0.00013

The largest percentage of radium was recovered from the bone marrow. The affinity of the radium to the bony structures makes it a haemostimulant "par-excellence."

Thorium-X on account of its exceedingly short life time is never deposited in the bones. Its toxicity does not permit its injection in doses greater than 20 or 40,000 mache units. According to Arneth these doses should never be exceeded either in pernicious anaemia or in other disease, as the effect of large doses cannot be judged beforehand. Messeth has reported two deaths in pernicious anaemia after the injection of 100,000 mache units intragluteal. If thorium-X has no effect in small doses given in short intervals, it should never be used at all, as we have no other substances which counteracts thorium-X. The animal experiments of da Silva Mello with thorium-X have shown that after a small but not fatal dose of thorium-X which causes no marked change in the blood picture the animals may die after the effect of thorium-X has entirely subsided. The autopsy findings in such animals are entirely negative. The accumulative effect of the thorium-X is further demonstrated by the animal experiments of da Silva Mello that after the injection of a second but not fatal dose of thorium-X in an animal which is still under the influence of the first injection a more intense action will be noted than if both doses were given at once In addition to this, thorium-X has a more injurious action upon the erythrocytes. Medium sized doses may cause a marked anisocytosis and a polychromatophilia of the erythrocyctes.

Radium on the other hand is a much less toxic agent. In fatal and superfatal doses given to animals it never produces an anisocytosis of the red cells and a complete leukopenia. It is not accumulative and doses up to one milligram (2,700,000 mache units) in either small or massive doses are without danger. We have thus far no death record after the injection of large doses of soluble radium salts. According to v. Noorden, radium is superior to thorium-X in the treatment of anaemia. It has a more selective action upon the erythropoetic component and a less injurious effect upon the leucocytes and myeloid tissue.

The advantage of radium over arsenic does not need to be emphasized. The toxicity of the arsenic no matter what preparation is used makes it desirable to replace it by an atoxic haemostimulant. A fraction of a milligram of soluble radium salt exerts a far more powerful effect upon the erythropoetic system without any untoward symptoms than arsenic even in large doses. Comparative investigations in the future have to decide if the present arsenic therapy will be replaced by radium.

REVIEWS AND ABSTRACTS.

Stephen Rushmore, M.D. (Boston). Progress in Gynecology. Boston Medical and Surgical Journal, CLXXIV, No. 8, pp. 277-282, Feb. 24, 1916. "Cancer and Radium. Much has been written on the use of radium in the treatment of cancer of the uterus, but the known results can be stated briefly. Ransohoff (Lancet-Clinic, Vol. cxiii, p. 289) advocates its use in inoperable cases, where it gives great relief. Some of these cases may prove later to be cured. He does not accept Kroenig's dictum that it should be used in every case to the exclusion of operation, though all acknowledge that the five-year limit only will show the final test."

"The line of treatment laid down by Ransohoff is in accord with the practice of most operators at the present time—to operate in cases in which the growth seems eradicable. While not in favor of pre-operative radiation on account of material increase in the difficulty of operation, he advocates post-operative treatment as a prophylactic measure against recurrence. If radium is effective for three and one-half centimeters only, even this range of applicability would cover most of the operable cases. If the carcinoma has advanced more than this distance the case is a border-line case, one of those which the surgeon so often wishes he had not attempted when he gets down to the growth."

"The report of the Radium Institute of London is to be recommended to those who desire detailed information and conservative views. An abridged report has been published giving a summary of the work of the past year. Pinch (Brit. Med. Jour., 1915, Part I, p. 367) the medical superintendent, says cancer of the uterus is very favorably affected by radium, both in inoperable and in operable cases, though it is not proper to speak as yet of a cure. Post-operative recurrences in the vagina are also favorably influenced. But if extensive operation has been carried out, great care is necessary in the post-operative use of radium, employing smaller amounts and thicker screens. Unless these precautions are observed, a severe and extensive destructive reaction may follow. This may be attributed to operative interference with the trophic nerves in the pelvis. If radium has been applied to the vagina, douches should be used night and morning for six weeks, at least, to prevent adhesive vaginitis. In some extremely susceptible cases a transient proctitis has been noted after the intravaginal treatment. For details of technic, reference must be made to original sources."

"Von Seuffert's (Strahlen Ther. Vol. iv, p. 740) experience in the treatment of cancer with radium, has been chiefly with reference to the treatment of cancer of the uterus, and he aims to give a fair statement of the present status of radium therapy as far as it is concerned with cancer. No method hitherto described gives as satisfactory immediate results in cancer of the uterus, whether the case is operable or inoperable. As to cures, no judgment can as yet be expressed."

"There can be no doubt that many inoperable cases can be so influenced that no evidence of carcinoma can be detected after treatment, and a number of such patients are now living one or two years after treatment who are clinically as if no cancer had ever been present. Among cases treated in the earlier period when radium was first used

there are a few free for over five years. Yet it is also to be noted that especially in the cases first treated the effect was very superficial owing to the technic, and that it is recognized now that the depth of the penetration is an important factor."

"If the disease has advanced to the glands, operation offers the hope of cure in some cases in which radium does not, for cases with such glandular metastases have survived operation for more than five years without recurrence, and tests of the penetration of radium indicate three and one-half centimeters as its limit. Bumm found glands with uninjured cancer cells after radium treatment. Bumm has also raised the question as to the injury or depression of vitality of cancer cells without evident microscopical injury, by reporting a case in which carcinoma nests were found up to the line of excision, yet the patient was well one and one-half years after operation with no evidence of carcinoma in or near the scar. But, if radium did not give quite as many cures, would it still not counterbalance the high operative mortality? Only time can tell. When we consider local effects, the limit of penetration of three and one-half centimeters gives at least as good a chance for cure as does operation."

"Through recent refinements in technic, the effects of radium in the body may be controlled so that there seems to be a so-called elective or specific action on carcinoma cells, though there is objection to the use of these terms in this relation. The progress which has already been made technically gives promise of still further improvement along the lines of lessening the dangers and increasing the efficiency. With deep penetration the danger is to the intermediate tissues."

"Allman (Strahlen. Ther., Vol. iv, p. 625) reports his experience in the treatment with radium, of inoperable carcinoma of the uterus, with results which are gratifying, when we consider the discouraging nature of this hopeless group. He comments adversely to the use of cholin, which has been so strongly recommended by some, on account of the disagreeable constitutional symptoms of which the patients complain."

"Cheron and Rubens-Duval (Strahlen. Ther., Vol. v, p. 80) report similar favorable results in a series of one hundred fifty-eight inoperable cases, one of which was cured (histological examination). One hundred and fifty-five showed regression, some of which are clinically cured, though less than five years. There were two in which treatment failed completely. These writers prefer massive doses, as do Kroenig and some others."

"The histological changes in the carcinomatous tissue are studied by Degrais and Bellot (Strahlen Ther., Vol. v, No. 1), whose article contains some microphotographs of the progressive destruction and final disappearance of the epithelial cells in the midst of connective tissue growth."

"Runge (Med. Klin., Vol. x, pp. 19, 59, 192) presents the replies to an 'Umfrage' or questionnaire, which was sent to a number of German gynecologists. The questions were:

(1) How do you regard radiotherapy for metropathies? (a) X-ray; (b) Radium or mesothorium.

(2) How do you regard radiotherapy for myomata? (a) X-ray; (b) Radium or mesothorium.

(3) How do you regard radiotherapy for cases of cancer of the female genitalia, and particularly in cancer of the uterus? (a) In-

operable; (b) Operable; (c) Recurrence; (d) Prophylactically after radical operation.

(4) What combination do you use in the radiotherapy of cases of uterine cancer? (a) X-ray alone, total dose given; (b) Radium or mesothorium alone, total dose given; (c) Combination of X-ray and radium or mesothorium, total dose given.

(5) What filtration of rays do you consider best, (a) for X-ray, (b) for radium or mesothorium.

"Sixteen replies to the questionnaire were received and may be briefly summarized."

"For metropathies at about the time of the climateric, X-ray gives excellent results in the hands of all who have tried it. Radium or mesothorium seems to be no better, not indicated, or more dangerous, though few had used them for this condition."

"For myomata, the results in general are very good if bleeding is the only symptom and no complications are present. But Fraenkel considers radiation more dangerous than operation, and von Herff says radiation is to be employed only if operation is contraindicated. Kroenig recommends radiation except in cases of younger women in whom enucleation is possible. In general, radium and mesothorium are not used for myomata."

"Radiation gives immediate results, which are favorable in most cases of inoperable cancer. Some replies are enthusiastic, others withhold judgment though all advocate giving it a trial."

"For operable cases all operate, except Kroenig, who operates only in selected cases (methods of selection not stated); Bumm, who says radiation gives certain local cure, and Pankow, who says that up to the present time, at least, radium has given good results."

"Results with recurrence are generally negative or unfavorable, though all try radiation if operation is impossible. Local recurrences do much better than glandular."

"Though prophylactic radiation is used by all (post operative), the general opinion is that not enough is known about results here to form a basis for judgment. In one reply it is said the questionnaire was sent out at least a year too soon."

"Myomata of the Uterus and Radium. Abbe (Med. Rec. Vol. lxxxvii, p. 379) reports a small series of cases of myomata of the uterus, which he had treated with radium (fifty to one hundred milligrams) at varying intervals, and had observed for a number of years. The tumors have diminished in size and in some cases almost disappeared, while in others no trace of the tumor remains on palpation. In one patient the mass filled the pelvis. Abbe has not seen harmful results with the technic he has employed, and now regards radium as the treatment of choice in all cases except pedunculated fibroids."……

"Kelly (Surg. Gyn. and Obst., Vol. xx, p. 271) presents some additional cases of fibroid of the uterus treated with radium with most satisfactory results. The size and position of the tumor seem to make little difference with the result, though the larger tumors show somewhat less tendency to disappear. The preferred method of application is intrauterine. The question of dosage is not yet solved satisfactorily, but in the later cases Kelly has had a tendency to use massive doses for shorter intervals, as he thinks this is less likely to disturb ovarian function."……

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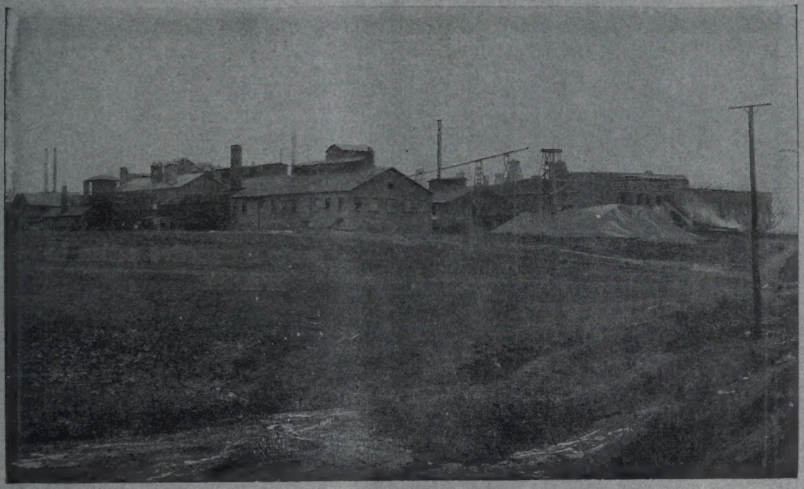

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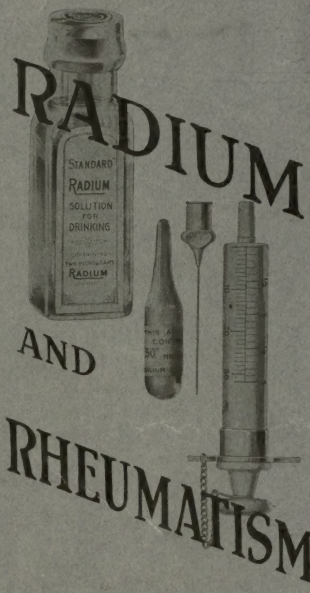

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